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Editorial

Is human rabies curable?

Human rabies is still a major problem in many developing countries of the world but it is seen rarely in Europe, North Americas and Australia. Over 55,000 annual cases occur worldwide according to WHO and this number may be low due to misdiagnoses and underreporting. Most patients in canine rabies endemic countries are diagnosed clinically without laboratory proof. Rabies is considered a virtually universally fatal disease. However, canines and possibly other mammals are thought to occasionally recover from infections with the rabies virus [1, 2]. Very few convincing human rabies survivors have been reported in the literature but they have generated hope that a cure can be found. Efforts to find treatments for human rabies go back to Celsius around AD 30 who recognized the infectious nature of rabies and the fact that it is transmitted via canine saliva. He recommended cupping and cauterizing wounds to prevent death. He did have another treatment suggestion: "place the patient in a river or lake head down till he can not avoid swallowing water". This must not have worked as he later acknowledged [3]. People in the middle ages turned to magic and prayer, usually to St Hubertus, the patron of hunters, fully recognizing that a horrible death is inevitable. After Louis Pasteur developed, what appeared to be an effective post-exposure prophylaxis in the 1880's, scientific efforts to heal patients with the disease began but were fruitless. Purging, bleeding, transfusing and a variety of then common local and systemic potions were tried but of no help.

As modern biotechnology evolved, serological and virucidal drugs as well as ICU care resulted in some transient symptomatic improvements and slight prolongation of life. Cases that present in western countries attract much attention from the media and are usually managed in ICUs with heroic efforts to sustain life. However, virtually all patients die, save a few that had post-exposure prophylaxis and survived for limited times and with severe disability.

Administration of alpha-interferon, anti-viral therapy with ribavarine, intravenous and intrathecal rabies immunoglobulin and multiple intradermal vaccinations after onset were all attempted by several investigators with no success [4]. A team at Chulalongkorn University Hospital, Bangkok administers 900 mL of human rabies immunoglobulin intravenously to a young female with early onset furious rabies. Her unstable circulatory status was stabilized and she converted into the paralytic from but became a "sleeping beauty" and died of respiratory complications. No neutralizing antibodies could be demonstrated in her CSF; showing that the blood-brain barrier remained intact. However, there have been a few convincing cases of human survival reported over the past 3 decades.

Case 1. A 6 year old boy in America was bitten by a bat in 1970. He was treated with a 15 day course of duck embryo rabies vaccine without immunoglobulin. He started to develop encephalitic symptoms that progressed to coma 20 days after having been bitten. Treatment was supportive. He developed high neutralizing rabies antibodies in both serum and CSF. A brain biopsy was obtained from his posteriorsuperior parietal lobe 2 weeks after onset of symptoms. It revealed encephalitis but no rabies virus could be identified. Efforts to isolate virus from saliva, brain and spinal fluid failed. He recovered fully after prolonged hospitalization and additional rehabilitation therapy [5].

Case 2. A 45 year old Argentinian woman was severely bitten by a dog in 1975. She received suckling mouse brain vaccine after a delay of 10 days but no immunoglobulin. Paralytic-like rabies symptoms developed 21 days later. She received supportive therapy only but recovered after prolonged convalescence over a period of 75 days. No virus could be isolated but she had developed huge neutralizing antibody titers in serum and CSF [6].

Case 3. A 32 year old laboratory technician, who had rabies pre-exposure vaccination, incurred an accidental laboratory inhalation exposure to rabies virus in 1977 at New York. He received only supportive care, developed very high neutralizing antibody titers in serum and CSF and no virus could be isolated throughout his prolonged clinical course. He recovered but with severe neurological sequele [7].

Case 4. A 9 year old Mexican boy was severely bitten by a dog in 1992, had a course of Purified Vero Cell rabies vaccine without immunoglobulin and developed furious rabies. He also developed high antibody titers in serum and CSF and no virus could

be isolated. He was treated with supportive care and survived for 4 years with severe neurological sequele [8].

Case 5. An Indian 6 year old girl incurred severe bites from a street dog. She was started on a course of purified chick embryo cell rabies vaccine without immunoglobulin. Symptoms of furious rabies developed 20 days later. She was found to have high and increasing neutralizing antibody titers in serum and CSF but no virus could be isolated. She received supportive care only and recovered with severe neurological sequele [9].

Case 6. Great hope was created when a 16 year old American girl was admitted with signs of furious rabies in 2005. She had been bitten by a bat and had not received any post-exposure prophylaxis. She was found to have very high neutralizing antibodies in serum and CSF shortly after admission, and no virus could ever be isolated. She was treated with induced deep coma therapy, ketamine, midozolam, ribavarine and amantadine and recovered almost fully [10].

Fascinating is also the report by EH Follmann et al. from the University of Alaska at Fairbanks who surveyed native fox trappers for the presence of neutralizing rabies antibodies (suggesting asymptomatic or abortive rabies infection). Their report contains the case of an elderly professional trapper of foxes who collected over 3,000 pelts over 47 years in a fox rabies endemic region. He had never had any rabies vaccination and yet had a neutralizing antibody level of 2.30 IU/ml indicating significant contact with rabies virus and possibly an abortive or undetected infection.

Finding high titers of neutralizing rabies antibody in serum and CSF shortly after onset of clinical signs is rare. Following repeated efforts, virus can usually be isolated from saliva, spinal fluid, urine and from neck skin biopsies. The six known survivors of rabies all had neutralizing serum and CSF antibody soon after onset of symptoms. No virus could ever be isolated from their saliva, CSF or tissues. This is a strong argument that they managed to control the virus by mounting a very early and effective neutralizing antibody response.

What can we conclude and apply in our future treatment plans for human rabies? Rabies must still be considered a virtually invariably fatal disease. Any future efforts to provide curative care for human rabies should focus on patients who arrive prior to onset of coma and who have an early vaccine induced or endogenous antibody response soon after onset (neutralizing antibody titers in serum and CSF). Such patients should be admitted to an ICU, appropriately sedated using barbiturates and/or benzodiazepines, have their fluid, electrolyte and cardio-pulmonary systems supported and receive high grade nursing care. This was done with cases 1-5. These were patients who survived the acute illness with or without serious sequels and without the use of antivirals or brainwave suppressive deep anesthesia. A basic supportive treatment plan can be implemented at any tertiary care hospital at affordable cost in staff time and funding. Experimental treatment with new drugs and biologicals should only be attempted after having been proven in animal models and by centers that have the multispecialty staff and facilities to tackle such a complex task.

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